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Improved Outcomes by Integrated Care of Anticoagulated Patients with Atrial Fibrillation using the simple ABC (Atrial Fibrillation Better Care) Pathway

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None.

AUTHORS' CONTRIBUTION

MP and GYHL conceived and performed the analysis, interpreted data, drafted and finalized the manuscript. GFR assisted in data preparation and analysis and critically revised the manuscript. BO and DAL provided substantial contribution with critical revision of the manuscript. All authors have access to the data presented and approved the final version of the manuscript.

ABSTRACT

Background: An integrated care for the clinical management of atrial fibrillation patients is advocated as a holistic way to improve outcomes; the simple **ABC** (Atrial fibrillation Better Care) pathway has been proposed for this. The ABC pathway streamlines care as follows: **'A' A**void stroke; **'B' B**etter symptom management; **'C' C**ardiovascular and **C**omorbidity optimisation.

Methods: We performed a post-hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial**.** An 'integrated care' approach was defined according to the ABC pathway. Patients fulfilling all criteria were categorized as the 'ABC' group; those not fulfilling all criteria were the 'non-ABC' group. Trial-adjudicated all-cause death, composite outcome of stroke/major bleeding/cardiovascular death and first hospitalization were the main outcomes.

Results: Among the 4060 patients in the original cohort, 3169 (78.0%) had available data to compare integrated care (ABC; n=222; 7.0%) vs. 'non-ABC' (n=2947; 93.0%) management.

Over a median [IQR] follow-up of 3.7 [2.8-4.6] years, Atrial fibrillation patients managed with integrated care (ABC group) had lower rates for all the outcomes (all p<0.001), compared to the non-ABC group. A Cox multivariable regression analysis showed that atrial fibrillation patients managed in the ABC group had a significantly lower risk of all-cause death (HR 0.35; 95%CI 0.17-0.75), composite outcome (HR 0.35; 95%CI 0.18-0.68) and first hospitalization (HR 0.65, 95%CI 0.53-0.80).

Conclusions: The simple ABC pathway allows the streamlining of integrated care for atrial fibrillation patients in a holistic manner and is associated with a lower risk of adverse outcomes (including mortality, stroke/major bleeding/cardiovascular death and hospitalization).

Keywords: atrial fibrillation, ABC pathway, comorbidities, integrated care, outcomes.

INTRODUCTION

Atrial fibrillation has a major impact on quality of life and major adverse clinical events (i.e. stroke, major bleeding, cardiovascular death, hospitalizations)[1,2]. In the last decade, overall clinical management of these patients has drastically changed, leading to improved outcomes, particularly stroke prevention[1,2].

Apart from the increased risk of stroke, atrial fibrillation is also associated with significant mortality and more hospitalisations. Of the deaths associated with atrial fibrillation, only approximately 1 in 10 are stroke-related, while up to 7 in 10 are cardiovascular-related[3–5]. Atrial fibrillation patients are afflicted by several comorbidities (both cardiovascular and non-cardiovascular), which may relate to the high cardiovascular and all-cause mortality, despite the improvements in oral anticoagulant (OAC) drug use[5–7]. Hence, more integrated pathways of atrial fibrillation care have been advocated, to take account of both atrial fibrillation-specific and non-specific clinical factors[8]. Such an integrated care approach significantly reduces cardiovascular-related hospitalizations and the risk of all-cause death[9].

Nevertheless, a streamlined simple approach to atrial fibrillation management is required. The **ABC** (Atrial fibrillation Better Care) pathway has been proposed as a possible approach to the holistic management of atrial fibrillation patients in an integrated manner[10]. The ABC pathway streamlines care as follows: **'A' A**void stroke (with **A**nticoagulants); **'B' B**etter symptom management, with patient-centred decisions on rate or rhythm control; **'C' C**ardiovascular and **C**omorbidity risk optimisation[10].

We hypothesised that an integrated care approach, based on the ABC pathway, would significantly reduce clinically relevant outcomes (including mortality, stroke/major bleeding/cardiovascular death and hospitalization) in patients with atrial fibrillation. To test this hypothesis, we performed a post-hoc analysis of a cohort derived from a high-quality randomized controlled trial, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial**.**

METHODS

The AFFIRM trial was a prospective randomized controlled trial investigating the difference in clinical outcomes of rate-control versus rhythm-control in the management of patients with atrial fibrillation (ClinicalTrials.Gov Identifier: NCT00000556), as described in detail elsewhere[11,12]. The present analysis is based on post-hoc AFFIRM database analyses, approved by the University of Missouri Institutional Review Board (IRB); the database was obtained from the National Institute of Health. The IRB for every participating centre approved the study protocol and all patients entered the study after providing written informed consent. The study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

Cohort Definition and Study Exposure

In order to verify the study hypothesis, we compared an integrated care approach, based on the ABC pathway, versus the standard care for atrial fibrillation patients.

The integrated care group (ABC group) were defined according to the criteria summarised in Figure 1. For the 'A' criterion, we considered optimal control of OAC therapy (vitamin K antagonist therapy only at the time of AFFIRM) as time in therapeutic range [TTR] ≥70%, which is optimizes thromboprophylaxis. For the 'B' criterion, we defined good symptom(s) control when the patient reported 2 or less symptoms among those considered in the AFFIRM trial at baseline (see Figure 1). For the 'C' criterion, only cardiovascular drugs use was available from the AFFIRM database, therefore we evaluated optimal pharmacological management of the main cardiovascular comorbidities (coronary artery disease, peripheral artery disease, stroke/transient ischemic attack, heart failure) according to current European recommendations as first line therapy[13]. For hypertension, we considered this as 'controlled' if baseline blood pressure values were ≤140/90 mmHg. For all the comorbidities considered, those optimally treated for all the conditions reported were defined as fulfilling the 'C' criterion.

Patients that fulfilled all criteria for integrated care were defined as the 'ABC' group, those who did not fulfill all criteria (i.e. fulfilling only 2, 1 or none of the ABC criteria) were defined as the 'non-ABC' group. Of the original 4060 patients enrolled in the AFFIRM trial, we considered all anticoagulated patients with available information to evaluate items included in the ABC pathway criteria.

Outcomes Definition

The main outcomes for this analysis were all-cause death, the composite outcome of stroke/major bleeding/cardiovascular death and first hospitalization. Based on the original AFFIRM protocol all adverse events were reported by each investigator and

centrally reviewed by an independent committee[11]. All deaths and embolic events were reviewed, with deaths adjudicated according to the main cause of mortality. Bleeding events were centrally reviewed for descriptive purposes. Patients' admission(s) to the hospital, as well as death and other major clinical adverse events, were reported at follow-up visits, that occurred every four months[11].

As secondary outcomes we considered the following: i) stroke; ii) major bleeding; iii) cardiovascular death; iv) first cardiovascular hospitalization; v) the occurrence of multiple hospitalizations; vi) total number of hospitalizations; vii) days of first hospitalization; and viii) total days of hospitalization. All outcomes were derived from the original follow-up case report forms.

Statistical Analysis

Following tests of normality, all continuous variables were reported as mean (SD, standard deviation) or median and interquartile range (IQR), as appropriate. Differences across the groups were evaluated with the t-test or Mann-Whitney U test, as appropriate. Categorical variables were expressed as counts and percentages and compared using the chi-square test.

Cumulative incidence of adverse events is shown using Kaplan-Meier curves, and compared across the groups with the Log-Rank test. Linear, logistic and Cox multivariable regression models were used according to the outcome considered. Linear logistic regression was used to examine the total number of hospitalizations, days of first hospitalization and total days of hospitalization. Logistic regression was used for occurrence of multiple hospitalizations, with Cox regression analysis

employed for all the other outcomes. All regression models were adjusted for age, gender, diabetes mellitus, hepatic/renal disease, pulmonary disease, first atrial fibrillation episode, and use of aspirin. The main analyses included comparisons between the ABC group (i.e. integrated care) vs. the non-ABC group for the main trial-adjudicated outcomes. Secondary analyses considered the comparisons within the non-ABC care subgroup of patients with 'part-ABC' care (i.e. fulfilling 2 out of 3 criteria, i.e. AB, BC, AC) against patients completely fulfilling all ABC care criteria. Finally, we also examined the relationship between the total number of ABC criteria fulfilled and occurrence of the main outcomes. Thus, we analysed the relationship between incompletely fulfilling integrated care (i.e. with only 2 out of 3 ABC criteria fulfilled, i.e. AB, BC, AC) compared to 'suboptimal care' (with only 0 or 1 ABC criteria fulfilled), to full integrated care (i.e. ABC group).

Additional sensitivity analyses were conducted including only patients with high thromboembolic risk (CHA_2DS_2-VASc score ≥2). A two-sided p-value <0.05 was considered statistically significant. All analyses were performed using SPSS v. 25.0 (IBM, NY, USA).

RESULTS

Among the original 4060 patients enrolled in the AFFIRM trial, 3169 (78.0%) were anticoagulated and had available data to compare integrated care (ABC group; n=222; 7.0%) vs 'non-ABC' (n=2947; 93.0%) management approaches [Table 1]. Patients managed with integrated care (ABC group) were *less likely* to be female and affected by hypertension (p=0.014), comorbidities (p<0.001) and polypharmacy

(p<0.001). At baseline, use of aspirin was less common among atrial fibrillation patients in the ABC care group (p=0.001). The ABC group had lower median CHA_2DS_2-VASc score than the non-ABC care group (p<0.001) and significantly better TTR (p<0.001)

Follow-Up Analysis

Over a median [IQR] follow-up of 3.7 [2.8-4.6] years, patients managed with integrated care (ABC group) had lower rates of all-cause death (3.2% vs. 11.1%, p<0.001), the composite outcome (4.1% vs. 14.0%, p<0.001) and first hospitalization (44.6% vs. 63.4%, p<0.001), compared to the non-ABC group (Table 2). As secondary analyses, the ABC group also had a lower rate of major bleeding (p=0.004), cardiovascular death (p=0.001) and first cardiovascular hospitalization (p<0.001), as well as a lower rate of both multiple and total hospitalizations (both p<0.001). Both median number of first hospitalization days and total hospitalization days were lower in the ABC group (both p<0.001).

Survival Analysis and Regression Models

The cumulative risks of all-cause death, composite outcome and first hospitalization were significantly lower in patients managed with an integrated care approach (ABC group) compared to the non-ABC group [Figure 2]. For the secondary outcomes, no difference was found in the cumulative risk of stroke [Figure S1], but there were significantly lower risks for major bleeding (Log-Rank: 7.115, p=0.008), cardiovascular death (Log-Rank: 8.394, p=0.004) and first cardiovascular hospitalization (Log-Rank: 16.876, p<0.001) [Figures S2-S4].

Cox multivariable regression analysis showed that use of integrated care (ABC group) was independently associated with a lower risk of all-cause death (hazard ratio [HR]: 0.35, 95% confidence interval [CI]: 0.17-0.75), the composite outcome (HR: 0.35, 95% CI: 0.18-0,68) and first hospitalization (HR: 0.65, 95% CI: 0.53-0.80) compared to non-ABC care. The ABC group was also associated with a lower risk of major bleeding, cardiovascular death and first cardiovascular hospitalization (Table 3).

On logistic regression analysis, an integrated care approach (ABC group) was associated with a lower risk of multiple hospitalizations (odds ratio: 0.38, 95% CI: 0.26-0.56). Linear regression analysis demonstrated that the ABC approach was associated with significantly lower total hospitalizations ($p<0.001$) and total days of hospitalization ($p=0.008$) (Table 3).

Number of ABC criteria fulfilled and Outcomes

We analysed the relationship between incompletely fulfilling integrated care (i.e. with only 2 out of 3 ABC criteria fulfilled, i.e. AB, BC, AC) compared to suboptimal care (0-1 ABC criteria fulfilled), to full integrated care (i.e. ABC group). Kaplan-Meier curves showed progressively lower cumulative risks across the groups, from suboptimal care to AB, BC, AC and full integrated care (ABC group) for all-cause death ($p<0.001$) and the composite outcome ($p<0.001$) [Figures S5, S6].

For the first hospitalization outcome, the ABC group, and the anticoagulated (i.e. AB and AC) groups had significantly lower risk compared to the non-anticoagulated BC group and suboptimal care group ($p<0.001$) [Figure S7].

Cox regression analysis (Table 4) showed a progressively lower risk of all-cause death and the composite outcome from suboptimal care to AB, BC, AC and fully integrated care (ABC group). For the first hospitalization outcome, the three part-ABC strategies showed a similar risk reduction, with full-integrated ABC care demonstrating the large relative risk reduction (42%) (Table 4).

Lastly, we analysed the relationship between numbers of ABC criteria fulfilled and the risk of major adverse outcomes. Kaplan-Meier curves showed a progressively lower cumulative risk for all the main outcomes going from none to all ABC criteria fulfilled (all $p<0.001$) [Figure S8-S10]. Cox regression analysis confirmed a progressively lower risk with increasing number of ABC criteria for all outcomes (Table 5).

Sensitivity Analysis

We conducted a sensitivity analysis limited to only atrial fibrillation patients with a high thromboembolic risk (CHA_2DS_2-VASc ≥2). This analysis found that the integrated care approach (ABC group) was associated with a significantly lower risk for all the main and secondary outcomes, consistent with the main analyses (Table S1).

DISCUSSION

In this post-hoc analysis of a clinical trial cohort of anticoagulated patients with atrial fibrillation, we have demonstrated that an integrated care approach based on the simple ABC pathway criteria was associated with a significantly lower risk of clinically relevant outcomes (including mortality, stroke/major bleeding/cardiovascular death and hospitalization), as well as lower risks of hospitalization and cardiovascular hospitalization. The risk of multiple and total hospitalizations was lower, as was the duration of total days of hospitalization. With a progressively greater application of integrated care components based on the ABC pathway, there was a progressively lower risk of trial-adjudicated clinically relevant outcomes (including mortality, stroke/major bleeding/cardiovascular death and hospitalization).

For the management of atrial fibrillation patients, there has necessarily been much focus on stroke prevention as the priority, but this only represents one component of an integrated or holistic approach to managing patients with atrial fibrillation. OAC with vitamin K antagonists (VKA, e.g. warfarin) significantly reduces stroke and systemic thromboembolism (by 64%) and all-cause mortality (by 26%) when compared to placebo or control [14]. If VKAs are used, attention to quality of anticoagulation control, as expressed by TTR, is crucial as TTR is a major determinant of major adverse outcomes[15–19]. In the AFFIRM trial, the only OAC used was warfarin, and a high TTR has been associated with improved outcomes[15,20]. Where TTR is poor, contemporary management has the option of using the non-VKA OACs (NOACs), given the relative efficacy, safety and convenience of these drugs compared to the VKAs[2], although geographical differences in NOAC uptake are evident[21] and drug adherence of these relatively short-acting OACs is important[22].

In relation to decision-making regarding rate or rhythm control strategies, decisions should be made based on patient-centred and symptom-directed reasons. Rate control and rhythm control strategies are non-inferior in relation to adverse outcomes such as mortality, stroke and hospitalisation[23]. The main benefit of rhythm control in the short-term appears to be improvement in symptoms and functional capacity[24], although one published small trial of catheter ablation in atrial fibrillation patients with heart failure (CASTLE-AF) suggested a possible benefit regarding mortality and hospitalisations[25]. Presented results from the CABANA trial[26] comparing drug therapy against catheter ablation showed non-inferiority for the primary outcome on an intention-to-treat analysis, although symptomatic improvement was evident in those randomised to catheter ablation.

Nevertheless, many atrial fibrillation patients are elderly and have multiple comorbidities[6,27,28]. Indeed, the risk of cardiovascular death and all-cause death are common outcomes in patients with atrial fibrillation[3–5,7,29]. In an analysis from the ROCKET-AF trial, for example, the majority of deaths related to atrial fibrillation were cardiovascular and related to associated comorbidities[3]. In the Loire Valley Atrial Fibrillation project, over a 2.5 years follow-up observation, 14% of patients died, with the majority of deaths associated with pre-existing cardiovascular comorbidities rather than stroke[5]. Apart from proactive management of comorbidities, attention also needs to be focused on lifestyle modification in atrial fibrillation patients, including obesity, alcohol excess, regular exercise, etc[30].

All these aspects of atrial fibrillation patient management, including stroke prevention, optimization of heart rate and symptoms with rate or rhythm control, and

precipitants/comorbidity management have been referred to as the 'domains of atrial fibrillation management' in the 2016 European guidelines[31]. In a recent systematic review and meta-analysis, an integrated care approach as part of a holistic and comprehensive atrial fibrillation management plan, resulted in a significantly reduction in all-cause death and cardiovascular hospitalization[9]. The 6th Atrial Fibrillation Network (AFNET)/European Heart Rhythm Association (EHRA) consensus conference also underlined the need for developing an "integrated atrial fibrillation clinic", based on atrial fibrillation nurse and dedicated cardiologist which could be able to implement the main atrial fibrillation management domains[32].

Nevertheless, approaches to provide integrated care have varying complexity[8]. The ABC pathway was proposed with the aim to provide simple guidance for the main components of integrated care, helping to streamline the interventions, decision-making and optimize the patient management pathway[10]. The ABC pathway has been incorporated into our regional primary care guidance for atrial fibrillation detection and management issued by the West Midlands Academic Health Sciences Network (WMAHSN) in England (http://www.clinitecs.uk/primary-care-clinical-pathway-for-atrial-fibrillation-detection-management).

The present analyses clearly demonstrate that an integrated approach based on the ABC pathway was associated with reduction in mortality, stroke/major bleeding/cardiovascular death and hospitalization, but not stroke risk. In the systematic review by Gallagher and colleagues, integrated care also showed no significant effect on stroke occurrence[9]. The strong impact on the main adverse outcomes with the ABC pathway even in patients at high thromboembolic risk, in

addition to our demonstration that a progressive fulfilment of ABC components was associated with a progressively lower risk of adverse outcomes, substantiates and strengthen the concept that a holistic approach or integrated management for atrial fibrillation patients is associated with a significant benefit on patient outcomes.

Limitations

First, the post-hoc analysis of this study represents the main limitation, together with limited power to detect differences across not pre-specified groups. Second, the modest number of subjects and events in the integrated care (ABC) group limits the generalizability of our results. However, the strong reduction in risk seen despite the limited numbers would suggest that compliance with the ABC pathway is associated with a positive effect on patient outcomes. Third, patients included in the non-ABC group appeared to be more complex from a clinical perspective, with multiple comorbidities. Conversely, given the high prevalence of comorbidities in the non-ABC group, we can speculate that full implementation of the ABC pathway may result in even an even greater reduction in risk. Lastly, since the original AFFIRM study clinical practice and guideline recommendations have evolved significantly over the last decade. Nonetheless, the high quality of data gathered by the original AFFIRM study as well as the *trial-adjudicated outcomes* represents a clear strength of the current analyses. While this study represents a first piece of evidence about the effective role of the simple ABC pathway in improving outcomes in atrial fibrillation patients, future prospective trials are needed to support and confirm our results and are currently ongoing.

CONCLUSION

The simple ABC pathway allows the streamlining of integrated care for atrial fibrillation patients in a holistic manner and is associated with a lower risk of adverse outcomes (including mortality, stroke/major bleeding/cardiovascular death and hospitalization) in a clinical trial cohort of anticoagulated patients with atrial fibrillation.

DISCLOSURES

MP has received small consulting fee from Boehringer Ingelheim; BO has been consultant for Lundbeck, Amarin, Boehringer Ingelheim; DAL reports educational grants from Bristol-Myers Squibb and Boehringer Ingelheim, speaker activity for Pfizer, and consultant activity for Bristol-Myers Squibb, Bayer and Boehringer Ingelheim; GYHL has served as consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees are received personally. Other authors have no disclosures to declare.

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FIGURE LEGENDS

Figure 1: The ABC Pathway definitions applied to the AFFIRM Cohort

Legend: Symptoms considered were: chest pain, diaphoresis, diuresis, dizziness, dyspnoea, oedema, fast heart rate, fatigue, orthopnoea, palpitations, panic, paroxysmal nocturnal dyspnoea, syncope, other symptoms; ACEi= angiotensin-converting enzyme inhibitor; ßBs= beta-blockers; CAD= coronary artery disease; HF= heart failure; HTN= hypertension; LLD= lipid lowering drugs; PAD= peripheral artery disease; TIA= transient ischemic attack; TTR= time in therapeutic range.

Figure 2: Kaplan-Meier Curves according to the Integrated Care use

Legend: Solid Black Line= Integrated Care (ABC Group); Grey Dotted Line= non-ABC Care.

Table 1: Baseline Characteristics according to the Use of Integrated Care

	Non-ABC care	**Integrated Care (ABC Group)**	**p**
	N= 2947	**N= 222**	
Age *years*, median [IQR]	70 [65-76]	70 [65-75]	0.302
BMI *kg/m²*, median [IQR] *1978*	28.2 [25.0-32.1]	28.0 [24.5-31.4]	0.236
Female sex, n (%)	1177 (39.9)	60 (27.0)	<0.001
Hypertension, n (%)	2102 (71.3)	141 (63.5)	0.014
Diabetes Mellitus, n (%)	589 (20.0)	36 (16.2)	0.173
Smoking , n (%)	358 (12.1)	20 (9.0)	0.164
Coronary Artery Disease, n (%)	1155 (39.2)	9 (4.1)	<0.001
Myocardial Infarction, n (%)	517 (17.5)	6 (2.7)	<0.001
Peripheral Arterial Disease, n (%)	200 (6.8)	2 (0.9)	0.001
Stroke/TIA, n (%)	427 (14.5)	4 (1.8)	<0.001
Heart Failure, n (%)	678 (23)	6 (2.7)	<0.001
Valvular Heart Disease, n (%)	381 (12.9)	20 (9.0)	0.090
Hepatic/Renal Disease, n (%)	148 (5)	10 (4.5)	0.733
Pulmonary Disease, n (%)	404 (13.7)	23 (10.4)	0.159
First AF Episode, n (%) *3083*	938 (32.9)	78 (35.5)	0.446
Randomized Treatment, n (%)			0.778
Rate Control	1604 (54.4)	123 (55.4)	
Rhythm Control	1343 (45.6)	99 (44.6)	
Use of Aspirin, n (%)	736 (25.0)	36 (16.2)	0.003
Comorbidities, median [IQR]	2 [1-3]	1 [1-2]	<0.001
Polypharmacy, n (%) *3165*	1173 (39.9)	49 (22.1)	<0.001
CHA_2DS_2-VASc, median [IQR]	3 [2-4]	2 [1-3]	<0.001
TTR *%*, median [IQR]	65.9 [49.9-79.8]	82.2 [76.1-89.3]	<0.001

Legend: AF= atrial fibrillation; BMI= body mass index; IQR= interquartile range; TIA= transient ischemic attack; TTR= time in therapeutic range.

Table 2: Outcomes rates according to the Use of Integrated Care

	Non-ABC Care	**Integrated Care (ABC Group)**	**p**
	N= 2947	**N= 222**	
All-Cause Death, n (%)	326 (11.1)	7 (3.2)	<0.001
Composite Outcome, n (%)	412 (14.0)	9 (4.1)	<0.001
Stroke, n (%)	111 (3.8)	6 (2.7)	0.418
Major Bleeding, n (%)	178 (6.0)	3 (1.4)	0.004
Cardiovascular Death, n (%)	185 (6.5)	2 (0.9)	0.001
First Hospitalization, n (%)	1868 (63.4)	99 (44.6)	<0.001
First Cardiovascular Hospitalization, n (%)	1088 (36.9)	48 (21.6)	<0.001
Multiple Hospitalizations, n (%)	1053 (35.7)	36 (16.2)	<0.001
Total Hospitalizations, median [IQR]	1 [0-2]	0 [0-1]	<0.001
First Hospitalization Days, median [IQR]	4 [2-8]	3 [2-7]	<0.001
Total Hospitalization Days, median [IQR]	9 [4-18]	5 [2-11]	<0.001

Legend: IQR= interquartile range.

Table 3: Regression Models for the Use of Integrated Care in Relation to Outcomes

	Integrated Care (ABC) vs. Non-ABC Care*	
	HR (95% CI)§	p
All-Cause Death	0.35 (0.17-0.75)	0.006
Composite Outcome	0.35 (0.18-0.68)	0.002
Stroke	0.90 (0.39-2.06)	0.804
Major Bleeding	0.26 (0.08-0.81)	0.021
Cardiovascular Death	0.17 (0.04-0.70)	0.014
First Hospitalization	0.65 (0.53-0.80)	<0.001
First Cardiovascular Hospitalization	0.57 (0.43-0.77)	<0.001
	OR (95% CI)#	p
Multiple Hospitalizations	0.38 (0.26-0.56)	<0.001
	Std. Beta†	p
Total Hospitalizations	-0.098	<0.001
First Hospitalization Days	-0.034	0.142
Total Hospitalization Days	-0.061	0.008

Legend: *Adjusted for age, gender, diabetes mellitus, hepatic/renal disease, pulmonary disease, first AF episode, use of aspirin; §Cox regression model; #Logistic regression model; †Linear regression model; AF= atrial fibrillation; CI= confidence interval; HR= hazard ratio; OR= odds ratio.

Table 4: Relationship between ABC Pathway Components and Outcomes

	All-Cause Death*	**Composite Outcome***	**First Hospitalization***
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Standard Care	Ref.	Ref.	Ref.
Only A-B Criteria	0.72 (0.48-1.08)	0.75 (0.53-1.07)	0.64 (0.54-0.75)

Only B-C Criteria	0.64 (0.37-1.09)	0.68 (0.43-1.09)	0.77 (0.63-0.92)
Only A-C Criteria	0.42 (0.24-0.76)	0.48 (0.31-0.77)	0.71 (0.60-0.85)
Integrated Care (All ABC Criteria fulfilled)	0.31 (0.15-0.67)	0.32 (0.16-0.62)	0.58 (0.47-0.71)

Legend: *Adjusted for age, gender, diabetes mellitus, hepatic/renal disease, pulmonary disease, first AF episode, use of aspirin; CI= confidence interval; HR= hazard ratio.

Table 5: Relationship between Total Number of ABC Criteria Fulfilled and Outcomes

	All-Cause Death*	**Composite Outcome***	**First Hospitalization***
	HR (95% CI)	HR (95% CI)	HR (95% CI)
No ABC Criteria fulfilled	Ref.	Ref.	Ref.
At least One ABC Criteria fulfilled	0.70 (0.55-0.90)	0.73 (0.59-0.91)	0.73 (0.65-0.81)
At least Two ABC Criteria fulfilled	0.49 (0.35-0.67)	0.54 (0.40-0.71)	0.56 (0.50-0.64)
Integrated Care (All ABC Criteria fulfilled)	0.25 (0.12-0.55)	0.26 (0.13-0.52)	0.47 (0.38-0.59)

Legend: *Adjusted for age, gender, diabetes mellitus, hepatic/renal disease, pulmonary disease, first AF episode, use of aspirin; CI= confidence interval; HR= hazard ratio.

Highlights

- The ABC pathway streamlines integrated care of atrial fibrillation patients
- Integrated care, according to ABC pathway, is associated with lower risk of adverse events.
- There was lower mortality, stroke/bleeding/cardiovascular death and hospitalization.
- Use of the ABC pathway allows holistic and integrated management of atrial fibrillation patients.

Figure 1

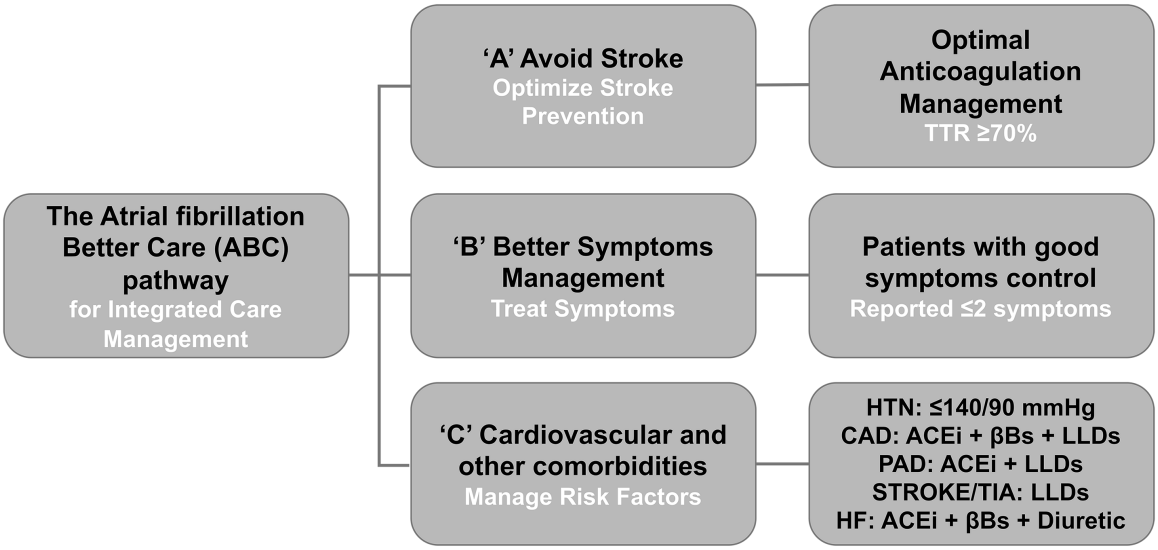
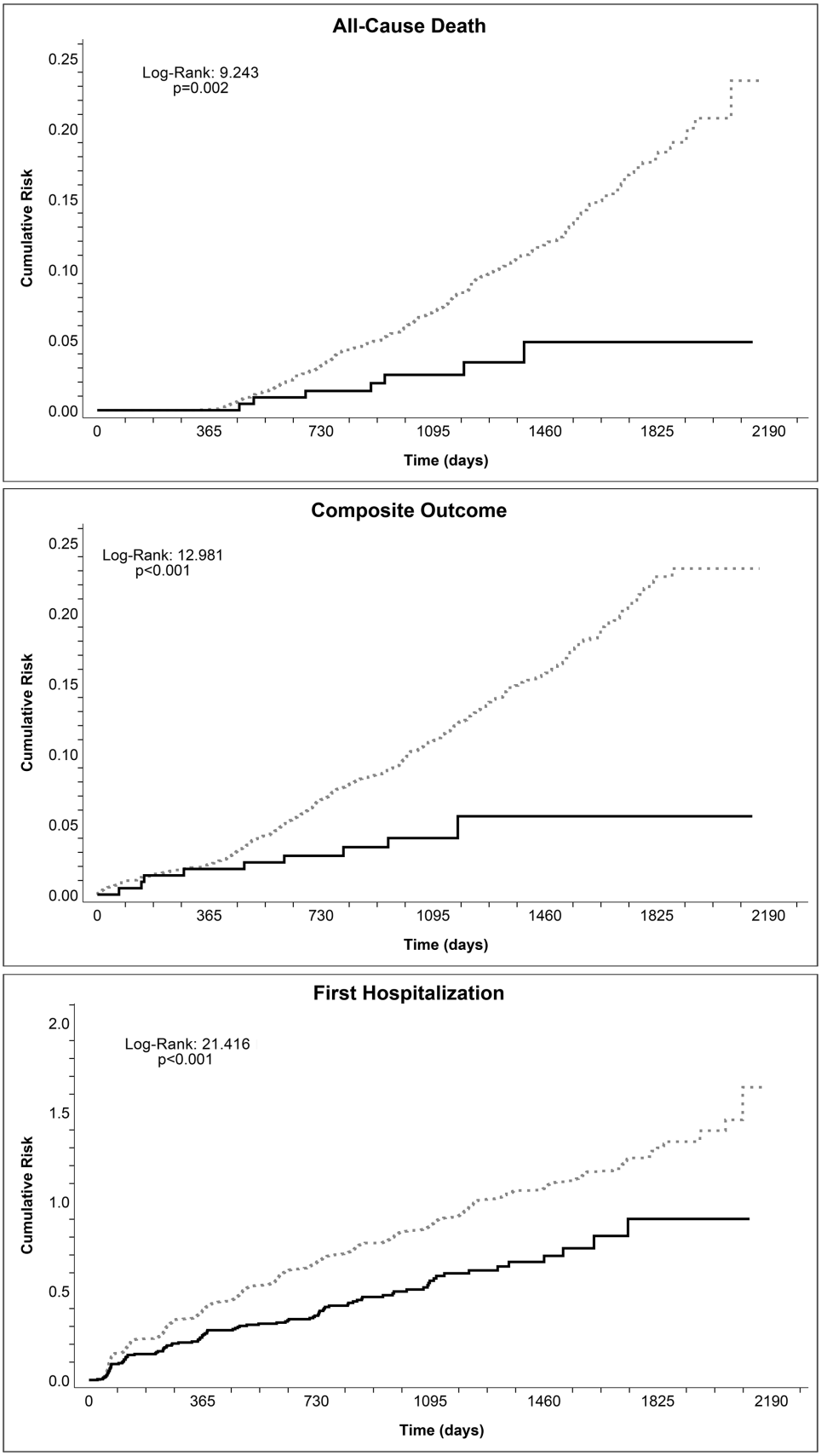

The Atrial fibrillation Better Care (ABC) pathway
for Integrated Care Management
'A' Avoid Stroke
Optimize Stroke Prevention
Optimal Anticoagulation Management
TTR ≥70%
'B' Better Symptoms Management
Treat Symptoms
Patients with good symptoms control
Reported ≤2 symptoms
'C' Cardiovascular and other comorbidities
Manage Risk Factors
HTN: ≤140/90 mmHg
CAD: ACEi + βBs + LLDs
PAD: ACEi + LLDs
STROKE/TIA: LLDs
HF: ACEi + βBs + Diuretic

Figure 2


All-Cause Death
Log-Rank: 9.243
p=0.002
Cumulative Risk
0.25
0.20
0.15
0.10
0.05
0.00
0
365
730
1095
1460
1825
2190
Time (days)
Composite Outcome
Log-Rank: 12.981
p<0.001
Cumulative Risk
0.25
0.20
0.15
0.10
0.05
0.00
0
365
730
1095
1460
1825
2190
Time (days)
First Hospitalization
Log-Rank: 21.416
p<0.001
Cumulative Risk
2.0
1.5
1.0
0.5
0.0
0
365
730
1095
1460
1825
2190
Time (days)

Improved Outcomes by Integrated Care of Anticoagulated Patients with Atrial Fibrillation using the simple ABC (Atrial Fibrillation Better Care) Pathway

Marco Proietti, Giulio Francesco Romiti, Brian Olshansky, Gregory Y.H. Lip

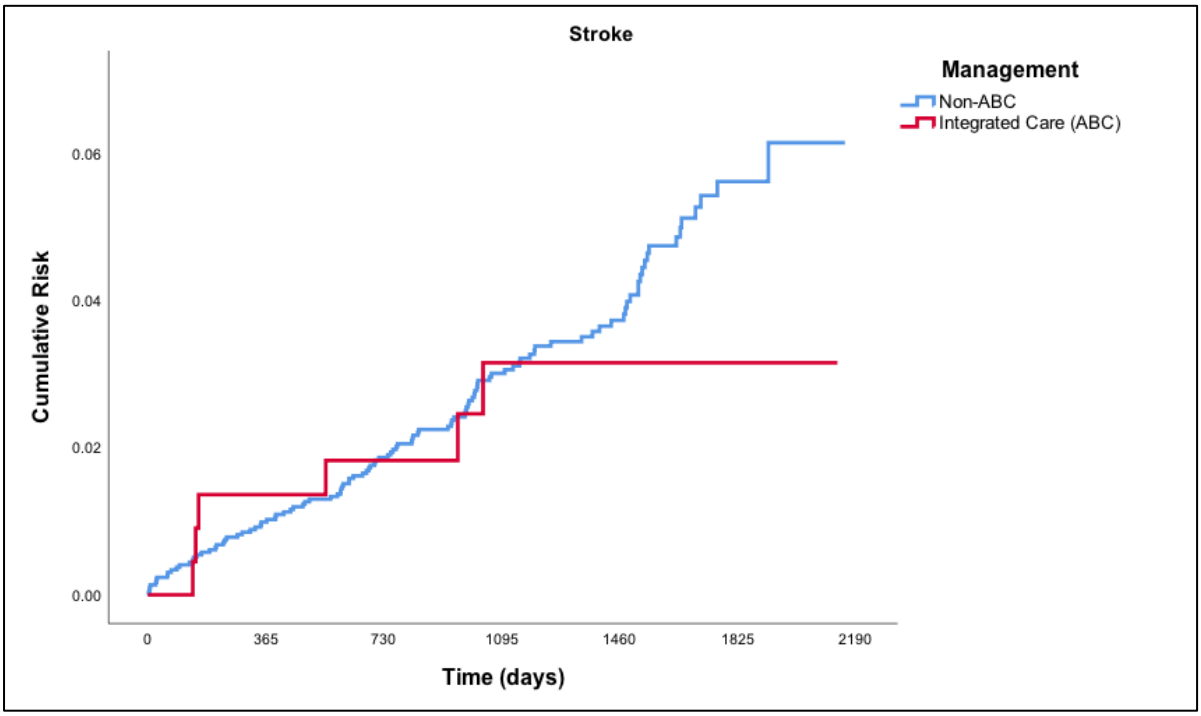
Supplementary Materials

Table S1: Sensitivity Analysis for Patients with CHA_2DS_2-VASc ≥2

	Integrated Care (ABC) vs. Non-ABC Care*	
	HR (95% CI)§	p
All-Cause Death	0.37 (0.17-0.84)	0.017
Composite Outcome	0.29 (0.13-0.65)	0.003
Stroke	0.90 (0.39-2.06)	0.804
Major Bleeding	0.26 (0.08-0.81)	0.021
CV Death	0.17 (0.04-0.70)	0.014
First Hospitalization	0.59 (0.46-0.75)	<0.001
First CV Hospitalization	0.55 (0.39-0.78)	0.001
	OR (95% CI)#	p
Multiple Hospitalizations	0.39 (0.26-0.61)	<0.001
	Std. Beta†	p
Total Hospitalizations	-0.095	<0.001
First Hospitalization Days	-0.037	0.131
Total Hospitalization Days	-0.059	0.015

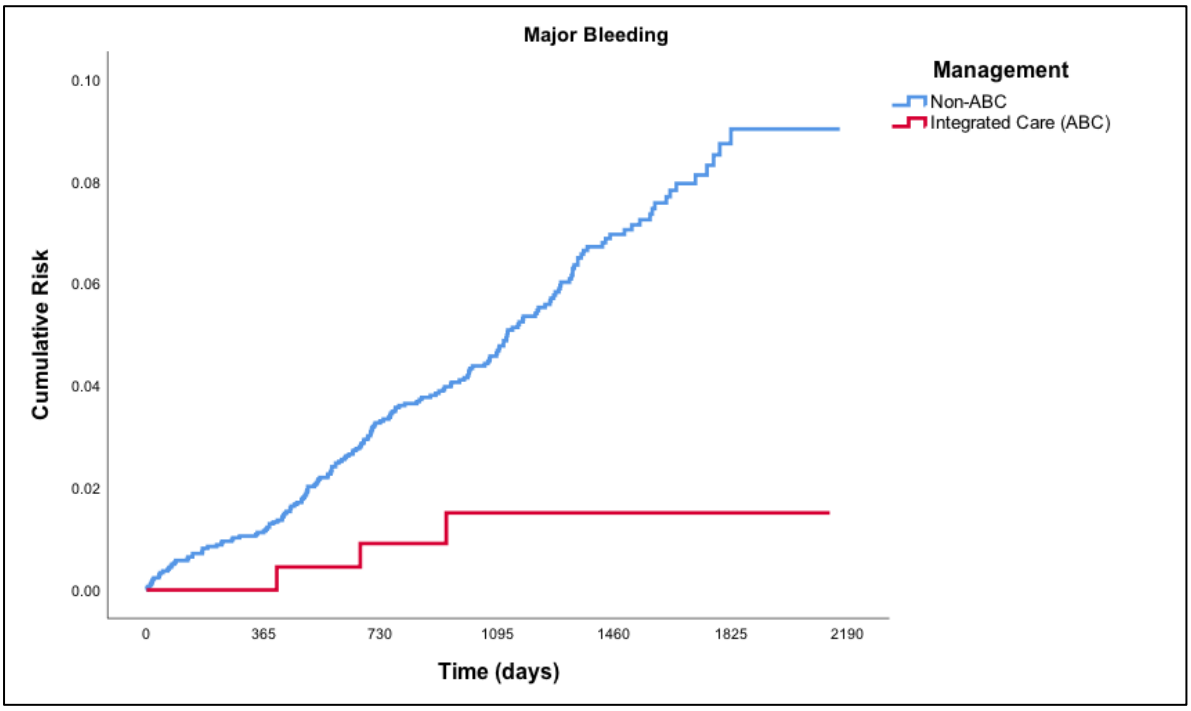
Legend: *Adjusted for age, gender, diabetes mellitus, hepatic/renal disease, pulmonary disease, first AF episode, use of aspirin; §Cox regression model; #Logistic regression model; †Linear regression model; AF= atrial fibrillation; CI= confidence interval; CV= cardiovascular; HR= hazard ratio; OR= odds ratio.

Figure S1: Kaplan-Meier about Stroke according to the type of care



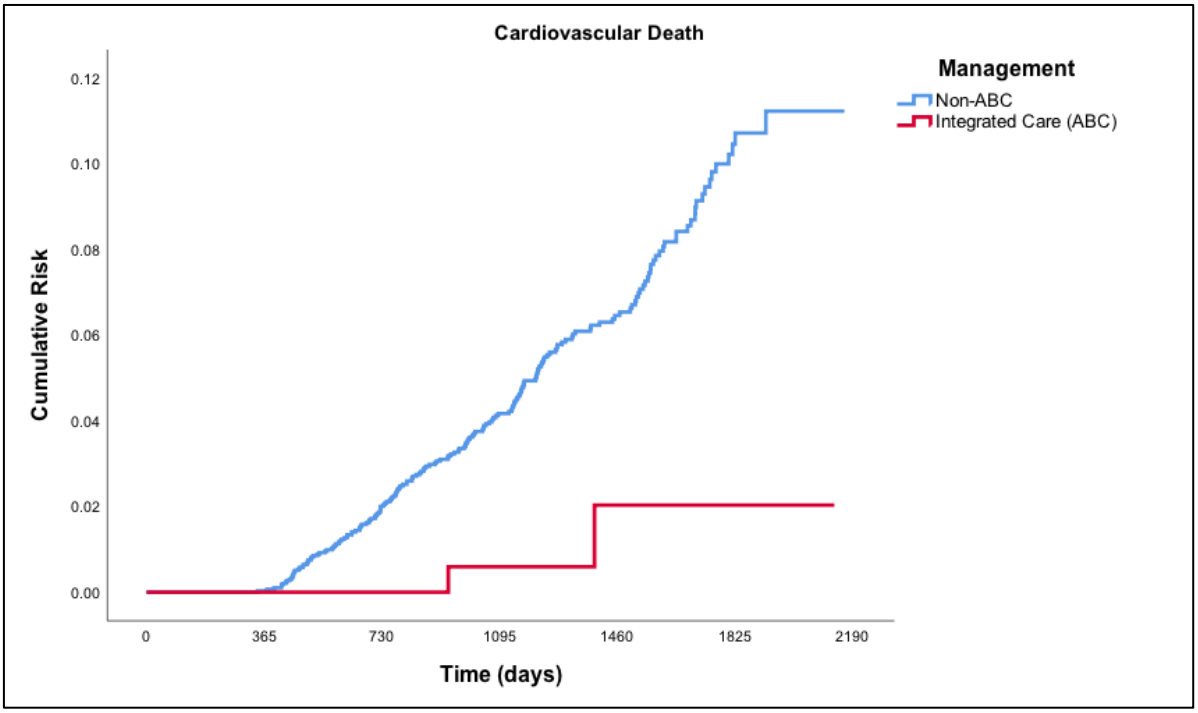
Legend: Log-Rank: 0.277, p=0.599

Figure S2: Kaplan-Meier about Major Bleeding according to the type of care



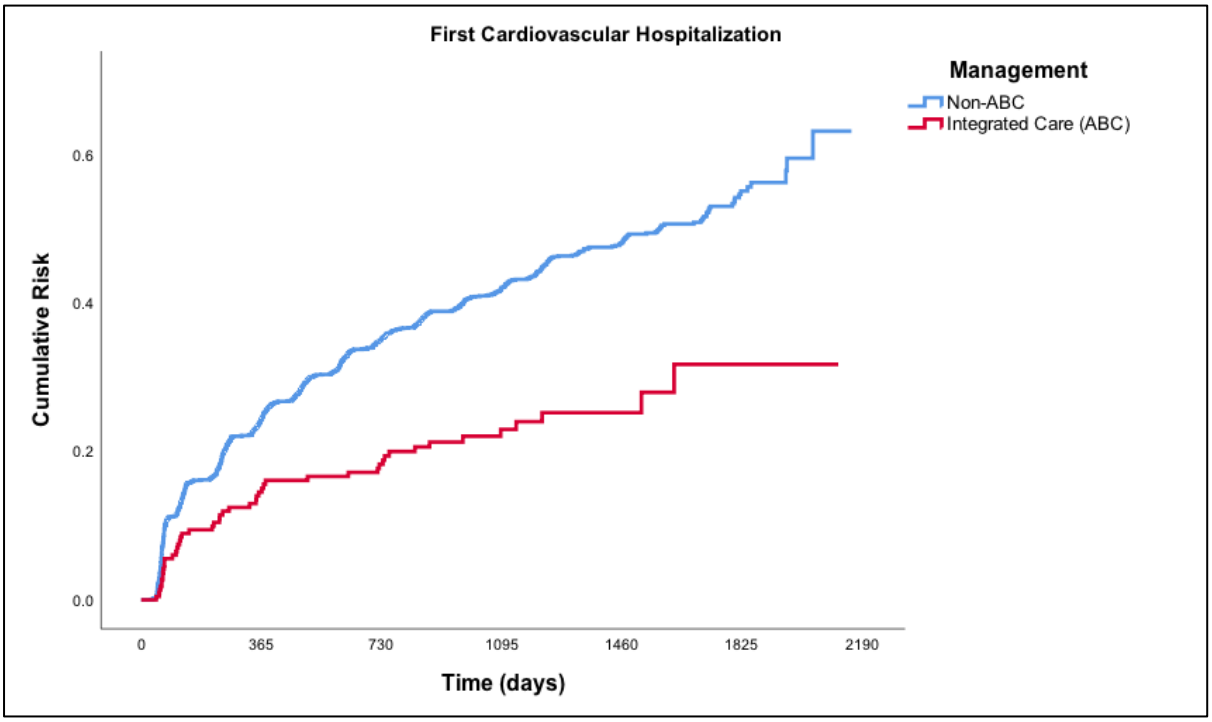
Legend: Log-Rank: 7.115, p=0.008

Figure S3: Kaplan-Meier about Cardiovascular Death according to the type of care



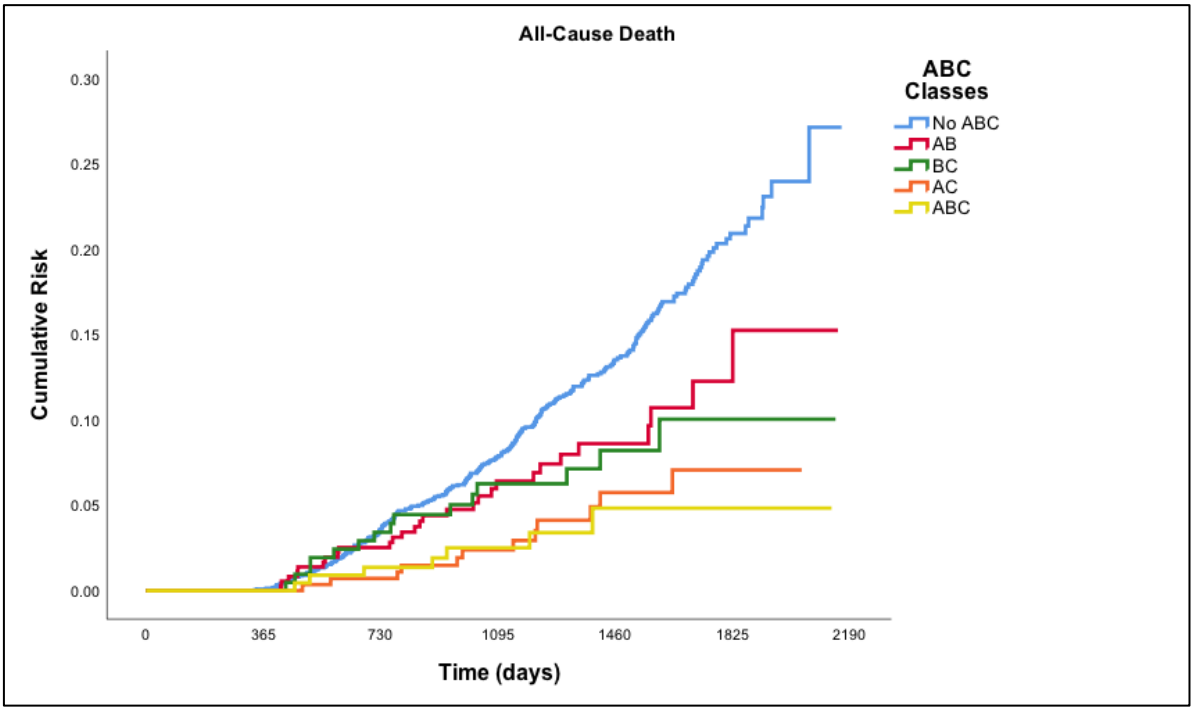
Legend: Log-Rank: 8.394, p=0.004

Figure S4: Kaplan-Meier about First Cardiovascular Hospitalization according to the type of care



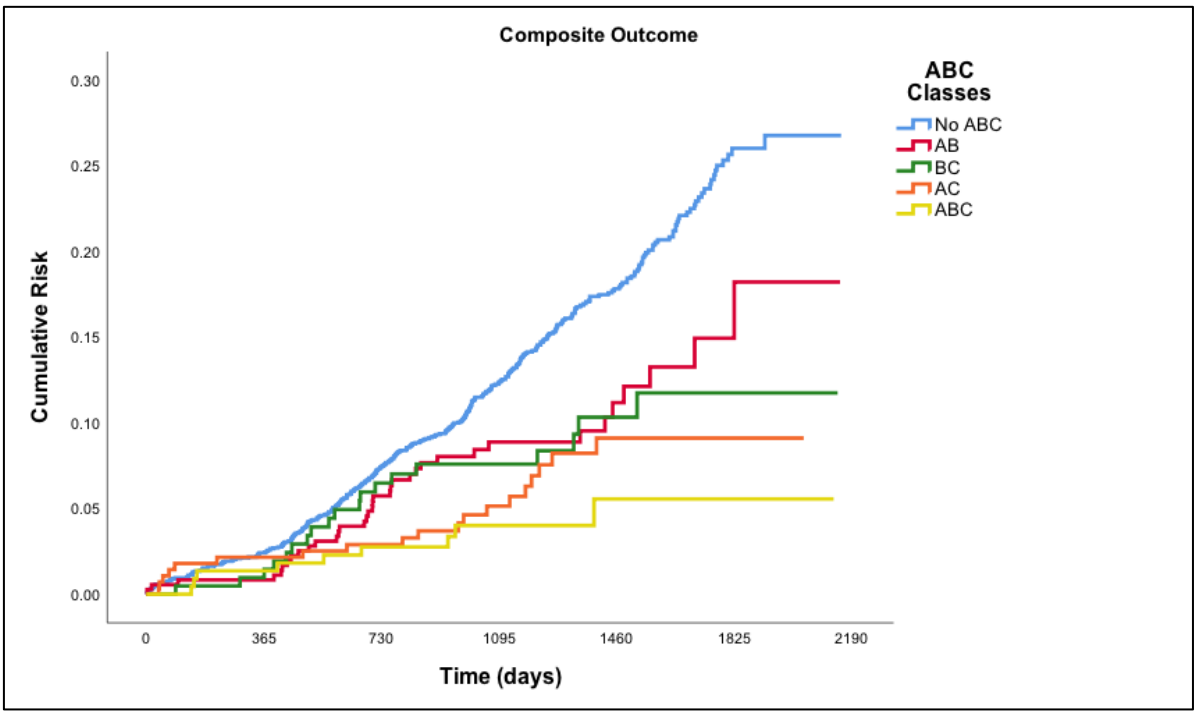
Legend: Log-Rank: 16.876, p<0.001

Figure S5: Kaplan-Meier about All-cause death according to level of integrated care



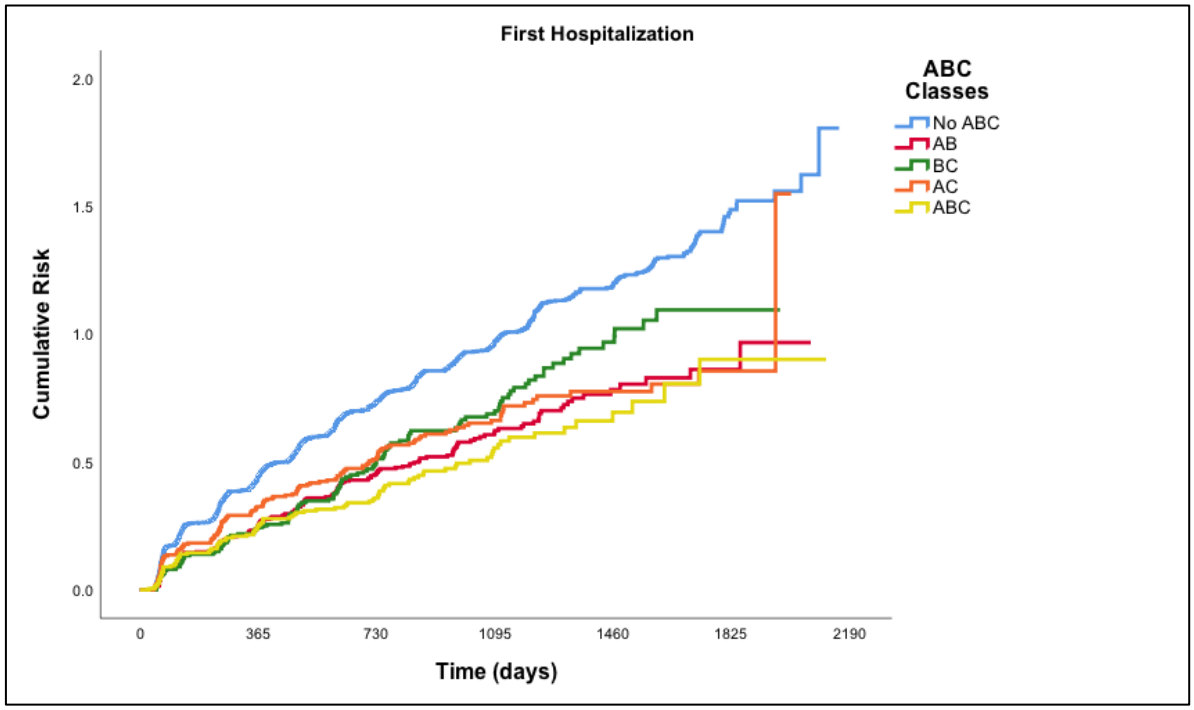
Legend: Log-Rank: 30.642, p<0.001

Figure S6: Kaplan-Meier about Composite outcome according to level of integrated care



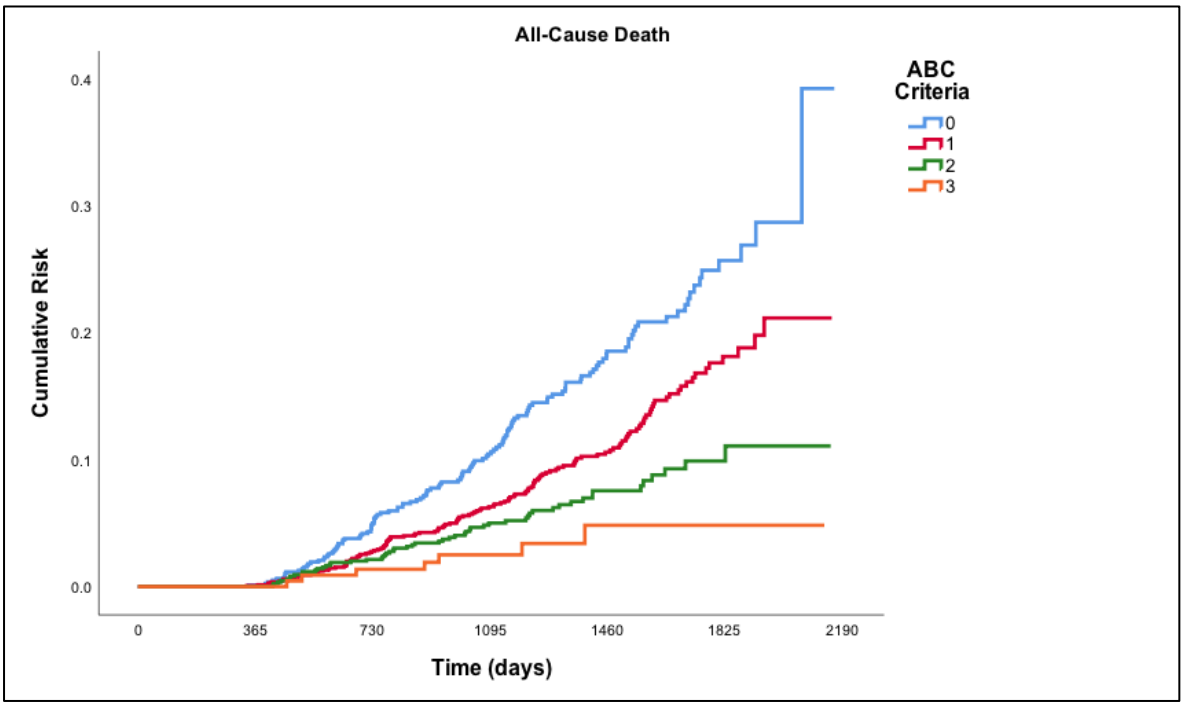
Legend: Log-Rank: 37.252, p<0.001

Figure S7: Kaplan-Meier about First hospitalization according to level of integrated care



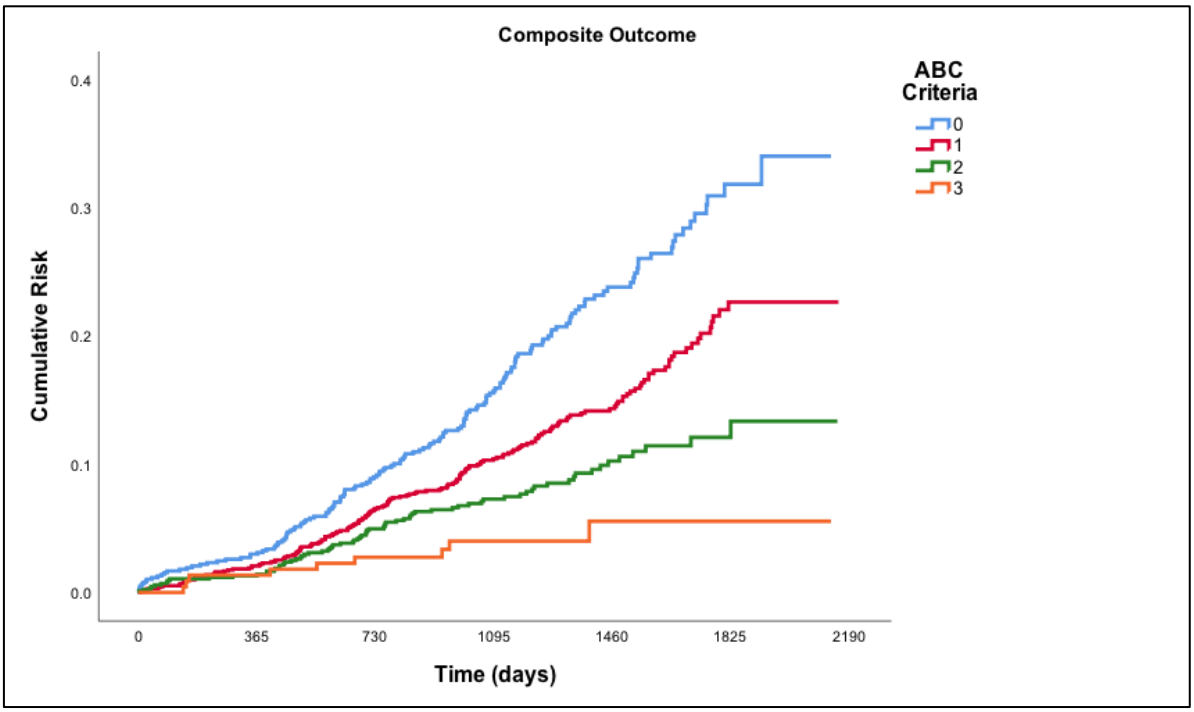
Legend: Log-Rank: 83.125, p<0.001

Figure S8: Kaplan-Meier about All-cause death according amount of ABC criteria



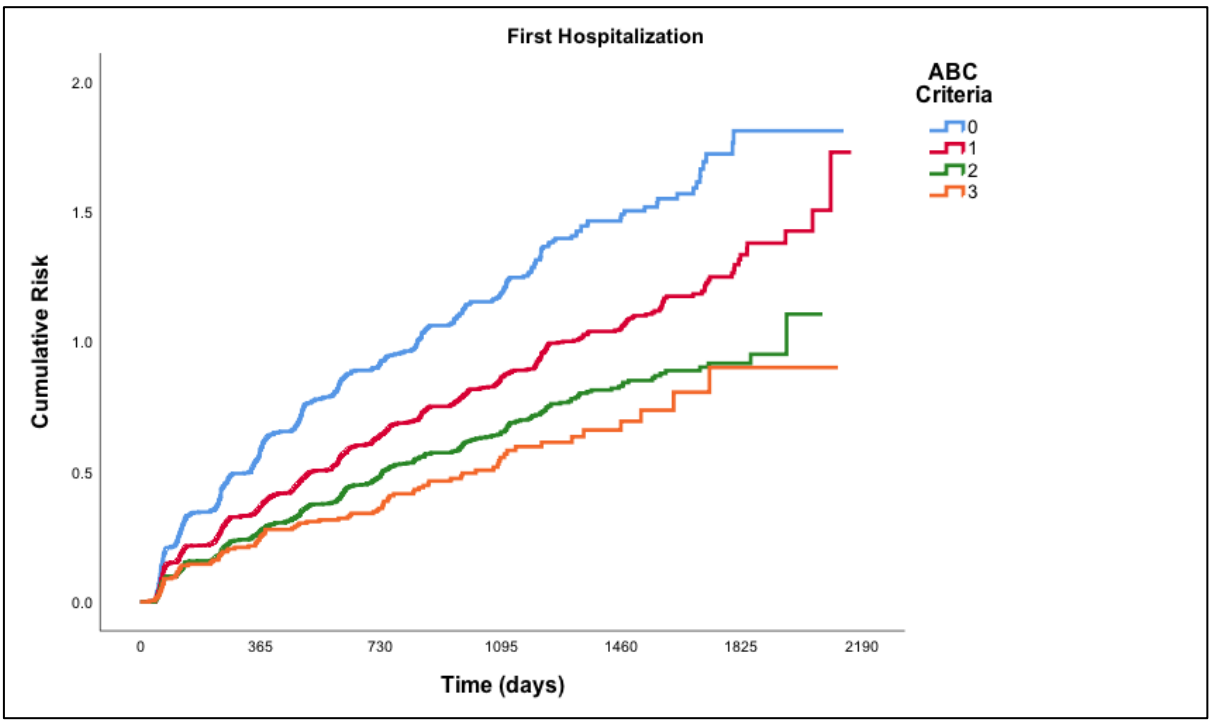
Legend: Log-Rank: 43.485, p<0.001

Figure S9: Kaplan-Meier about Composite outcome according amount of ABC criteria



Legend: Log-Rank: 52.907, p<0.001

Figure S10: Kaplan-Meier about First hospitalization according amount of ABC criteria



Legend: Log-Rank: 131.967, p<0.001